Complete Summary

GUIDELINE TITLE

ACR Appropriateness Criteria® staging of bronchogenic carcinoma.

BIBLIOGRAPHIC SOURCE(S)

Rozenshtein A, Reig B, Khan A, Movsas B, Bradley J, Gopal RS, Haramati LB, Jeudy J Jr, Komaki RU, Kong FM, MacMahon H, Mohammed TL, Rosenzweig KE, Kaiser L, Expert Panel on Thoracic Imaging. ACR Appropriateness Criteria® staging of bronchogenic carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2008. 10 p. [62 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Rozenshtein A, Davis SD, Ritsuko RU, Bradley JD, Gopal RS, Haramati LB, McLoud TC, Movas B, Rosenzweig KE, White CS, Kaiser LK, Schiller JH, Expert Panel on Thoracic Imaging and Radiation, Oncology-Lung Work Group. Staging of bronchogenic carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2005. 9 p.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Bronchogenic carcinoma, non-small-cell and small-cell lung carcinoma

GUIDELINE CATEGORY

Diagnosis
Evaluation

CLINICAL SPECIALTY

Internal Medicine
Nuclear Medicine
Oncology
Pulmonary Medicine
Radiology

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of initial radiologic examinations for patients with bronchogenic carcinoma, non-small-cell and small-cell lung carcinoma

TARGET POPULATION

Patients with bronchogenic carcinoma, non-small-cell and small-cell lung carcinoma

INTERVENTIONS AND PRACTICES CONSIDERED

1. X-ray, chest
2. Computed tomography (CT)
    - Chest, with or without contrast (including upper abdomen)
    - Abdomen, without and with contrast
    - Head, with contrast
3. Magnetic resonance imaging (MRI)
    - Head, with contrast
    - Chest, with contrast
4. Fluorodeoxyglucose-positron emission tomography (FDG-PET), whole body
5. Nuclear medicine (NUC), technetium (Tc)-99m bone scan, whole body

MAJOR OUTCOMES CONSIDERED

Utility of radiologic examinations in staging of bronchogenic carcinoma

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals, and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table

and narrative as developed by the topic leader(s). Questionnaires are completed by the participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1 to 9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by this Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The growing evidence that positron emission tomography (PET) is more accurate than computed tomography (CT) in staging of non-small-cell lung cancer (NSCLC) has prompted questions of its cost-effectiveness. A group of researchers conducted a meta-analysis of 12 individual studies in order to predict the most cost-effective strategy for staging of NSCLC patients in Canada. They concluded that addition of PET to CT is expected to save CA$1,455 per person. A more recent study calculated that routine fluorodeoxyglucose (FDG)-PET scanning with selective mediastinoscopy would save AU$2,128 per patient and would reduce inappropriate surgery.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Staging of Bronchogenic Carcinoma

Variant 1: Non-Small Cell Lung Carcinoma

Radiologic Procedure	Rating	Comments	RRL*
CT chest with or without contrast (including upper abdomen)	9	CT with contrast is preferred if there are no strong contraindications.	High
X-ray chest	8	Chest radiograph should be performed at the time of staging as baseline if no recent radiograph is available.	Min
FDG-PET whole body	8		High
MRI head with contrast	7	Particularly if neurological symptoms are present. See comments regarding contrast in the text below under "Anticipated Exceptions."	None
CT abdomen without and with contrast	5		High
CT head with contrast	5	If MRI is contraindicated and neurological symptoms are present.	Med
NUC Tc-99m bone scan whole body	5	Not necessary if PET has been done.	Med
MRI chest with contrast	3	Useful for evaluating chest wall invasion and for local staging of superior sulcus tumors.	None
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: Small Cell Lung Carcinoma

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9	Chest radiograph should be performed at the time of staging as baseline if no recent radiograph is available.	Min
CT chest with or	9	CT with contrast is preferred if there	High

Radiologic Procedure	Rating	Comments	RRL*
without contrast (including upper abdomen)		are no strong contraindications.	
MRI head with contrast	8	See comments regarding contrast in the text below under "Anticipated Exceptions."	None
FDG-PET whole body	7		High
CT abdomen without and with contrast	5		High
CT head with contrast	5	If MRI contraindicated and neurological symptoms are present.	Med
NUC Tc-99m bone scan whole body	5	Not necessary if PET has been done.	Med
MRI chest with contrast	2		None
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Non-Small Cell Lung Carcinoma

Staging

Staging of any tumor is done to determine the extent of disease. Staging information is important for two reasons: 1) to determine prognosis and 2) to select patients for surgical intervention and/or a different modality. The TNM staging system is widely used to classify lung tumors. In 1986, it was revised after epidemiologic evidence demonstrated improved survival following surgical resection in patients who had previously been classified as having unresectable disease. In the TNM classification, "T" indicates the features of the primary tumor, "N" indicates metastasis to regional lymph nodes, and "M" refers to the presence or absence of distant metastases (see Appendix 1 and 2 of the original guideline document).

The current Mountain classification consists of four stages which are defined in Appendix 2 of the original guideline document. Stage I has been divided into two

groups: IA and IB. Data have consistently shown a better outcome for patients with stage IA disease—that is, T1N0M0—than for any other subset. Survival rates are estimated to be approximately 60% in patients with clinical stage IA disease and only 38% for those in clinical stage IB. Stage IB is defined as patients with T2 tumors. Stage II is also subdivided into A and B groups. The survival rate for patients with stage IIA disease—that is, T1 lesions with involved hilar nodes (T1N1M0)—is higher than for those with stage IIB disease (T2N1M0 or T3N0M0). However, the former is a small group of patients who are encountered rather infrequently.

Stage III is divided into IIIA and IIIB, where IIIB is considered unresectable disease, (i.e., T4 and/or N3). In the current classification, tumors with limited invasion of the chest wall and mediastinum (T3) are considered to be potentially resectable provided that vital structures in the mediastinum, such as the great vessels, heart, and aerodigestive tract, are not involved. The designation T4 is now used to describe lesions with extensive invasion of the mediastinum or diaphragm, as well as tumors with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung. In the current system, patients with ipsilateral mediastinal and subcarinal nodal metastasis (N2) are also considered to have resectable cancer. However, for the most part, only patients with limited ipsilateral mediastinal nodal disease fall into the operable category. These are usually cases in which the tumor is contained within the capsule of the lymph nodes and is limited to involvement of the lower mediastinal nodes. A category N3 was added to the TNM staging to refer to metastasis in the contralateral mediastinal, hilar, scalene or supraclavicular lymph nodes. N3 disease is considered to be unresectable. In the current classification, stage IV includes patients with evidence of distant metastasis (M1) away from the ipsilateral primary tumor lobe of the lung.

A number of imaging modalities have historically been used in staging lung cancer. These have included standard and conventional tomography as well as computed tomography (CT) and magnetic resonance imaging (MRI). In some instances, accurate staging and the determination of appropriate treatment for patients with lung cancer can be made noninvasively with imaging modalities alone, although in most cases, some degree of surgical staging and biopsy evidence is also necessary.

Chest Radiographs

The need for appropriateness guidelines for routine chest radiographs in lung cancer appears to be a nonissue. The vast majority of primary lung cancers are initially detected on routine chest radiographs. There may be certain instances in which the chest radiograph alone is a sufficient imaging procedure for staging - for example, when an obvious metastatic bone lesion is detected or when large bulky contralateral mediastinal lymph nodes are present. However, numerous studies have shown that the chest radiograph lacks sensitivity in detecting mediastinal lymph node metastases and in detecting chest wall and mediastinal invasion.

Computed Tomography

CT has now become the major imaging modality of choice in the evaluation of patients with bronchogenic carcinoma. Numerous studies have shown that its value in staging is limited, because there are no morphologic criteria that would allow distinction between benign and malignant lymph nodes. It is certainly more sensitive than standard radiography, however, and it may serve as a guide to surgical management and in the determination of appropriate methods for surgical staging.

Traditionally, chest CT for staging of lung cancer is extended into the abdomen to include the adrenal glands. Whether this requires intravenous contrast material is debatable. One study addressed the question of whether administration of intravenous contrast material during CT of the thorax and upper abdomen (including the liver) changed the tumor stage and management compared with nonenhanced helical CT in 96 patients with newly diagnosed lung cancer. Although four of these patients were either upstaged or downstaged after intravenous contrast administration, there was no change in management. The authors concluded that contrast-enhanced CT extended to include the liver rarely adds to routine nonenhanced CT through the adrenal glands and does not influence management decisions.

Evaluation of Primary Tumor (the T Factor)

It is not always possible to distinguish T3 from T4 lesions with imaging studies. Lesions with chest wall invasion are classified as T3 lesions and are potentially resectable. Surgical resection, however, requires an en bloc resection of the pulmonary malignancy and the contiguous chest wall and is associated with an operative mortality in the range of 8 to 15%. It is therefore important to determine preoperatively if chest wall invasion is present in order to select patients as operative candidates. Although CT provides information incrementally superior to that of radiographs, many of the findings described in the literature that are said to be associated with chest wall invasion have been shown to be neither sensitive nor specific. One study demonstrated a sensitivity of only 62% for CT in distinguishing T3 to T4 tumors from T0 to T2 tumors. Similarly, another study found CT to be of limited value assessing chest wall invasion, with a sensitivity of 87% and specificity of only 59%. CT was found to be more specific in assessing chest pain (94%). Some of the signs that have been described include pleural thickening adjacent to the tumor, encroachment on or increased density of subpleural fat, or an obtuse angle between the pulmonary mass and the pleural surface. Only the presence of a mass in the chest wall or definite rib destruction are helpful indicators of chest wall invasion.

Similarly, CT may be useful when extensive mediastinal invasion is present. Contrast-enhanced images may show vascular encasement and involvement of major mediastinal organs. However, CT is unable in some instances to distinguish contiguity of tumor with the mediastinum from actual invasion of the walls of vital mediastinal structures. In one study the sensitivity of CT depended on the sign of mediastinal invasion that was used. It was only 40% for 90 degrees of contact between the mass and the mediastinal structure, and 44% if distortion of the mediastinal structure was present. Positive predictive values (PPVs) were low, and these authors concluded that CT was not useful in determining mediastinal invasion.

Evaluation of Nodal Metastasis (the N Factor)

CT is often the first-line method for assessing mediastinal nodes in bronchogenic carcinoma. Numerous studies have consistently documented improved survival of selected patients after resection of mediastinal nodal disease and, in most cases, adjuvant radiation therapy. The revised Mountain classification considers patients with ipsilateral mediastinal lymph node metastasis (N2) as having potentially surgically resectable stage IIIA disease. Included in this group are patients with 1) intracapsular rather than extracapsular involvement and 2) positive nodes identified at thoracotomy after negative mediastinoscopy. In addition, early reports have indicated that even patients with gross and bulky ipsilateral nodal metastasis (N2) may benefit from surgery if it is combined with neoadjuvant chemotherapy and radiation therapy. However, patients with contralateral mediastinal nodal involvement (N3) are considered to have unresectable stage IIIB disease.

Several studies have addressed the accuracy of CT in the staging of mediastinal nodal metastasis in lung cancer. More recent studies that have used total nodal sampling and the American Thoracic Society Lymph Node Classification have generally shown a low sensitivity of CT in detecting nodal metastasis.

A meta-analysis of mediastinal staging by CT evaluated 20 studies dated 1991 through 2001 with a total of 3,438 patients, with the vast majority using the short axis diameter >10 mm as the criterion for nodal positivity. Citing marked heterogeneity of the individual studies, the authors reported the pooled sensitivity and specificity of CT scanning as 57% and 82%, respectively, while the overall PPV and negative predictive value (NPV) of CT scanning were 56% and 86%, respectively. Furthermore, the authors concluded that there was no demonstrable improvement in accuracy over the past decade in spite of advances in CT technology.

In summary, controversy still exists about the value of CT scanning in staging the mediastinum in lung cancer. A negative CT scan for mediastinal adenopathy may provide useful information, particularly in institutions in which mediastinoscopy may not be available or preferred. If patients are selected immediately for thoracotomy without preceding mediastinoscopy, careful nodal sampling must be done at the time of surgery. Because of the low specificity of CT, enlarged lymph nodes must be biopsied for accurate staging. Despite the limited sensitivity and specificity of CT, it is used almost universally for staging the mediastinum in lung cancer. This use appears to be appropriate because of the additional information it provides, such as a map of enlarged nodes prior to mediastinoscopy, as well as information on enlarged nodes that are out of reach of the mediastinoscope or that are contralateral in position and suspect for N3 disease.

The issue of CT staging of the mediastinum in T1 lesions is controversial. T1 tumors are defined as lesions $\leq$3 cm in greatest diameter surrounded by lung or visceral pleura without evidence of invasion proximal to the lobar bronchus. Several studies have suggested a low prevalence of mediastinal nodal metastatic disease with T1 cancers (5%-15%). Because of this low prevalence, it has been suggested that CT may not be necessary in such patients and that the preoperative staging should be limited to plain chest radiographs. However, one study found a 21% prevalence of nodal metastasis among 104 patients with T1

lesions. The sensitivity of CT was 77% for detecting these metastases, and the study's authors recommended that CT be performed in such patients. Another study of 23 patients with T1 lesions found only one patient who had CT evidence of noncurative disease. Because of the low yield, CT was not recommended. In a larger series of 63 patients, the authors found that 14% of patients with T1 lung cancers had inoperable disease correctly detected by CT. However, pathologic proof of inoperability was lacking. In summary, the issue remains controversial, and none of the studies appears to be definitive.

Evaluation of Distant Metastasis (the M Factor)

The role of CT in determining extrathoracic metastasis from bronchogenic carcinoma is also controversial. There appears to be general agreement that CT of the thorax should include the adrenal glands, which are a frequent site of metastases from non-small cell lung cancer (NSCLC). In a study of 91 autopsy-proven adrenal metastases from lung cancer, the authors found that the sensitivity of CT was low (41%) but that the specificity was high (99%). They recommended CT but noted that patients with a negative CT had a 30% likelihood of adrenal metastasis. The other potential problem with screening the adrenal glands is the nonspecificity of the findings. This problem has been documented in later studies. Another study looked at 330 patients with bronchogenic carcinoma, 33 of whom had adrenal masses. Only 25% had metastatic disease, and the remainder had adenomas. Adenomas can often be distinguished from metastasis by their smaller size and low attenuation values. However, in many cases, additional imaging with MRI or percutaneous biopsy is necessary for diagnosis. A similar study confirmed the nonspecificity of adrenal masses in patients with nonadrenal primaries.

Bone scintigraphy has significant limitations in the detection of metastatic disease. Although it has high sensitivity, it is noted for very low specificity that ranges from 50 to 60%. Bone scintigraphy should probably be limited to cases in which patients have specified clinical indicators of bone metastasis. Routine cerebral imaging in the form of CT is recommended only for patients with stage III disease, particularly those with adenocarcinoma and large-cell carcinoma cell types.

Magnetic Resonance Imaging

Initial experience suggests that evaluation of the mediastinum with MRI is approximately equal to that of CT with regard to the staging of bronchogenic carcinoma. However, one study showed that MRI was significantly more accurate for detecting direct mediastinal invasion. Other studies have confirmed the usefulness of MRI, particularly in the evaluation of chest wall invasion and the local staging of superior sulcus tumors. One study showed an accuracy of MRI of 94% compared with 63% for CT in determining tumor invasion through the superior sulcus. Similarly, another study showed that T1-weighted images had 90% sensitivity and 86% specificity in detecting chest wall invasion by lung cancer. MRI is particularly useful in determining certain parameters of unresectability for superior sulcus cancers, such as invasion of the vertebral body and involvement of the subclavian artery and brachial plexus. The general conclusion of these studies is that MRI has advantages in the assessment of both chest wall and mediastinal invasion.

Positron Emission Tomography (PET)

Initial studies of PET imaging in lung cancer using 18-fluorodeoxyglucose (FDG) indicated that PET is clinically useful for staging lung carcinoma. The multicenter randomized PLUS (PET in lung cancer) trial, comparing a group of 96 patients staged with conventional workup with a group of 92 patients staged with both conventional workup and PET, concluded that "addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer." In a more recent study comparing PET to CT for nodal staging, the authors concluded that PET was more accurate than CT for N0, N2, and N3 disease, had a lower frequency of false-positive findings in the upper mediastinal nodes, and a lower frequency of false-negative findings in adenocarcinoma and false-positives in squamous cell carcinoma. However, addition of PET imaging in patients with negative brain CT or MRI does not appear to have much benefit. A recent study involving 287 patients with negative brain CT or MRI found four patients with positive PET findings. In all four patients brain metastases were excluded clinically.

The large body of evidence prompted several meta-analyses of the existing data. In a comprehensive review of current evidence, one meta-analysis pooled 18 studies conducted between 1994 and 2001 with the total of 1,045 evaluable patients. The authors found that the summary receiver operating characteristic (ROC) curve was significantly more accurate for PET than for CT ($p<0.001$), with a pooled sensitivity of 88% and a specificity of 89%. The PPV and NPV were 79% and 93%, respectively. A meta-analysis of 13 studies showed FDG-PET to be more accurate that CT in mediastinal lymph node staging of NSCLC.

Several studies compared the performance of FDG-PET with bone scintigraphy in patients with NSCLC and in patients with all types of lung cancer. In a prospective study of 48 patients with NSCLC, the authors demonstrated that the diagnostic sensitivity and accuracy of FDG-PET were 93.4% and 93.5%, respectively, compared to 92.5% and 72.5% for technetium (Tc)-99m MDP bone scans. They concluded that FDG-PET has the same sensitivity and a better accuracy than Tc-99m MDP bone scan to detect metastatic bone lesions in patients with NSCLC. In a retrospective study of 85 patients, the authors concluded that FDG-PET scans demonstrated significantly higher specificity and NPV than bone scans for evaluating bony metastases. A larger retrospective study in a group of 257 patients demonstrated the accuracies of PET and bone scan to be 94% and 85% ($p<0.05$), sensitivity values 91% and 75%, and specificity values 96% and 95%, respectively. The authors concluded that given the improvement in accuracy and sensitivity with PET, bone scan could be eliminated from the staging evaluation.

Availability of PET has improved dramatically in recent years. With over 1,000 cameras installed in North America in 2004, it is now feasible to include PET in the routine staging of lung carcinoma. PET may be particularly helpful in centers where mediastinoscopy is not readily available and in patients with significant comorbid conditions who are borderline candidates for surgery, with locally advanced disease, solitary brain metastasis, and cases of local recurrence that might qualify for repeat operation.

There is a mounting body of data supporting the utility of FDG-PET in the treatment of patients with NSCLC. One group of researchers investigated

prospectively the impact of FDG-PET on clinical management of patients with NSCLC. FDG-PET scanning changed or influenced management decisions in 70 (67%) of their 105 patients, prompting them to conclude that patients who underwent FDG-PET were frequently spared unnecessary treatment, and management was more appropriately targeted. Another group demonstrated in a study of 198 patients that systematic addition of FDG-PET had significant impact on patient management, altering diagnostic or therapeutic interventions in 72.2% and changing staging in 22.2% of patients. In a prospective randomized trial of patients with NSCLC, the authors demonstrated that addition of PET to the initial staging significantly decreased the number of mediastinoscopies.

The growing evidence that PET is more accurate than CT in staging of NSCLC has prompted questions of its cost-effectiveness. A group of researchers conducted a meta-analysis of 12 individual studies in order to predict the most cost-effective strategy for staging of NSCLC patients in Canada. They concluded that addition of PET to CT is expected to save CA$1,455 per person. A more recent study calculated that routine FDG-PET scanning with selective mediastinoscopy would save AU$2,128 per patient and would reduce inappropriate surgery.

Positron Emission Tomography/Computed Tomography

Since the resolution of PET imaging is relatively low, PET images are usually correlated visually with CT. The new integrated PET/CT technology is showing promise in staging lung carcinoma. Four recent studies involving a total of 1,073 patients showed that PET/CT ranged 42 to 85% in sensitivity, 84 to 100% in specificity, and 84 to 94% in accuracy. Two other studies demonstrated that PET/CT improves the accuracy of staging compared to PET and CT obtained separately. However, a retrospective review of 336 patients staged with PET (210) or PET/CT (126) demonstrated an increase in sensitivity (PET/CT 86%, PET alone 61%) at the price of decreased specificity (PET/CT 81%, PET alone 94%) and diminished accuracy (PET/CT 82%, PET alone 87%). The PPV of 69% for PET decreased to 56% for PET/CT, and the NPV of 92% for PET rose slightly to 95% for PET/CT. The authors concluded that improvements in PET technology have increased the sensitivity of integrated PET/CT at the cost of significantly decreased specificity and that noninvasive PET imaging is not ready to replace surgical staging in patients with NSCLC.

Small-Cell Lung Carcinoma

According to the recent analysis of the Surveillance, Epidemiology, and End Results database, small cell lung cancer (SCLC) now accounts for about 14% of all new cases of lung cancer. It is more aggressive than the non-small cell form, with median survival of 2-4 months if untreated. Rather than the TNM classification, the staging system widely applied is based on studies of the Veterans Administration Lung Study Group. In this system, patients are classified as having either limited disease (i.e., tumor confined to one hemithorax and to the regional lymph nodes) or extensive disease (i.e., tumor beyond this area in contralateral lung or extrathoracic sites). Extensive disease is present in 60 to 80% of patients newly diagnosed with SCLC. Conventional staging for extrathoracic metastasis in patients with SCLC includes CT of the abdomen, CT or MRI of the head, and bone scintigraphy. A bone marrow biopsy may be omitted for patients with normal blood counts, normal lactate dehydrogenase level, and negative result on bone

scan. Other routine staging procedures include liver function tests and complete blood counts.

Noninvasive imaging is generally recommended only in patients who have abnormal routine screening tests. One study compared CT and ultrasound (US) in staging the abdomen in patients with SCLC. They found that CT was more sensitive than US and showed 50% of patients with extensive disease compared with 39% by US. Twenty percent of patients were restaged as a result of the CT findings. These authors, however, recommended that CT of the abdomen only be performed in patients with biochemical abnormalities. In regard to the search for central nervous system (CNS) metastasis, again the recommendation is that routine brain CT or MRI only be done for patients involved in clinical study protocols. The remainder should be limited to patients with symptomatic or clinically detectable CNS metastasis. Another study attempted to determine the value of routine CT of the brain in patient with SCLC compared to neurologic findings. Of a total of 57 patients, both with and without neurologic symptoms, only four had brain metastasis, and three of these patients had the metastasis confirmed by CT. In the one negative patient, CT was later found to be positive. All of these patients were symptomatic or had positive neurologic examinations. Of the 54 non-neurologically symptomatic patients, no metastases were detected on CT.

As with NSCLC, skeletal metastasis may be evaluated with bone scanning. Although highly sensitive, bone scanning has a low specificity in SCLC, as it does in NSCLC. Two recent retrospective studies have suggested that PET can replace bone scintigraphy in staging patients with all types of lung cancer. Screening is best limited to patients with symptoms or abnormal biochemical profiles. A preliminary study of 25 patients examined the value of MRI in staging SCLC. The MRI resulted in a change in staging in 5 of the 25 patients. These patients were found to have extensive disease. Additional metastases were found in the bone and liver as a result of the MRI. However, details on the clinical studies on these patients are not available in this study, and the work appears to be too preliminary to allow any recommendation on the use of MRI in the staging of SCLC.

There is mounting evidence that PET is useful in staging SCLC patients. Several prospective studies each in a relatively small group of patients concluded that FDG-PET has high sensitivity for SCLC. In a larger prospective study, the authors demonstrated greater sensitivity of FDG-PET than that of CT for detecting extrathoracic lymph node involvement (100% versus [vs.] 70%, specificity 98% vs. 94%) and greater sensitivity and specificity for detecting distant metastases except to the brain (98% vs. 83%, specificity 92% vs. 79%). However, FDG-PET was significantly less sensitive than cranial MRI/CT in detecting brain metastases (46% vs. 100%, specificity 97% vs. 100%). In their sample, FDG-PET resulted in stage migration in 14 (12%) of 120 patients. All stage changes affected management. Only one patient was incorrectly staged by PET due to failure to detect brain metastases. The authors concluded that FDG-PET will improve staging and may reduce the number of tests and invasive procedures in patients with SCLC. Most recently, a group of authors demonstrated that FDG-PET changed management in 8% of their 63 SCLC patients and recommended FDG-PET as an initial staging tool for patients with this disease.

In a prospective study of patients with SCLC, the authors compared integrated PET/CT with standard staging (CT, bone scintigraphy, and bony marrow biopsy). In their group of 34 patients PET/CT resulted in changes of stage in 17%. Sensitivities for standard staging, PET, and PET/CT were 79%, 93%, and 93%, and specificities were 100%, 83%, and 100%, respectively. This group concluded that addition of integrated PET/CT could simplify and even improve staging in patients with SCLC.

Anticipated Exceptions

Nephrogenic systemic fibrosis (NSF, also known as nephrogenic fibrosing dermopathy) was first identified in 1997 and has recently generated substantial concern among radiologists, referring doctors and lay people. Until the last few years, gadolinium-based MR contrast agents were widely believed to be almost universally well tolerated, extremely safe and non-nephrotoxic, even when used in patients with impaired renal function. All available experience suggests that these agents remain generally very safe, but recently some patients with renal failure who have been exposed to gadolinium contrast agents (the percentage is unclear) have developed NSF, a syndrome that can be fatal. Further studies are necessary to determine what the exact relationships are between gadolinium-containing contrast agents, their specific components and stoichiometry, patient renal function and NSF. Current theory links the development of NSF to the administration of relatively high doses (e.g., >0.2 mM/kg) and to agents in which the gadolinium is least strongly chelated. The U.S. Food and Drug Administration (FDA) has recently issued a "black box" warning concerning these contrast agents (http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705HCP.pdf).

This warning recommends that, until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated glomerular filtration rate [GFR] <30 mL/min/1.73m^2), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s).

Abbreviations

- CT, computed tomography
- FDG-PET, fluorodeoxyglucose-positron emission tomography
- Med, medium
- Min, minimal
- MRI, magnetic resonance imaging
- NUC, nuclear medicine
- Tc, technetium

Relative Radiation Level	Effective Dose Estimated Range
None	0
Minimal	<0.1 mSv
Low	0.1-1 mSv

Relative Radiation Level	Effective Dose Estimated Range
Medium	1-10 mSv
High	10-100 mSv

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate radiologic imaging procedures for evaluation of patients with bronchogenic carcinoma, non-small-cell and small-cell lung carcinoma

POTENTIAL HARMS

- Compared to computed tomography (CT), positron emission tomography (PET) has a lower frequency of false-positive findings in the upper mediastinal nodes, and a lower frequency of false-negative findings in adenocarcinoma and false-positives in squamous cell carcinoma.
- Some patients with renal failure who have been exposed to gadolinium contrast agents (the percentage is unclear) have developed nephrogenic systemic fibrosis (NSF), a syndrome that can be fatal. The U.S. Food and Drug Administration (FDA) has recently issued a "black box" warning concerning these contrast agents. This warning recommends that, until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated glomerular filtration rate [GFR] <30 mL/min/1.73m^2), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s).

Relative Radiation Level (RRL)

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk

associated with an imaging procedure. Additional information regarding radiation dose assessment for imaging examinations can be found in the American College of Radiology (ACR) Appropriateness Criteria® Radiation Dose Assessment Introduction document (see "Availability of Companion Documents" field).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologist, radiation oncologist, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Rozenshtein A, Reig B, Khan A, Movsas B, Bradley J, Gopal RS, Haramati LB, Jeudy J Jr, Komaki RU, Kong FM, MacMahon H, Mohammed TL, Rosenzweig KE, Kaiser L, Expert Panel on Thoracic Imaging. ACR Appropriateness Criteria® staging of bronchogenic carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2008. 10 p. [62 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2008)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Thoracic Imaging and Radiation Oncology-Lung

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Anna Rozenshtein, MD; Beatriu Reig, MD; Arfa Khan, MD; Benjamin Movsas, MD; Jeff Bradley, MD; Ramesh S. Gopal, MD; Linda B. Haramati, MD; Jean Jeudy, Jr, MD; Ritsuko U. Komaki, MD; Feng-Ming Kong, MD, PhD, MPH; Heber MacMahon, MD; Tan-Lucien H. Mohammed, MD; Kenneth E. Rosenzweig, MD; Larry Kaiser, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Rozenshtein A, Davis SD, Ritsuko RU, Bradley JD, Gopal RS, Haramati LB, McLoud TC, Movas B, Rosenzweig KE, White CS, Kaiser LK, Schiller JH, Expert Panel on Thoracic Imaging and Radiation, Oncology-Lung Work Group. Staging of bronchogenic carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2005. 9 p.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria® radiation dose assessment introduction. American College of Radiology. 2 p. Electronic copies: Available from the American College of Radiology Web site.

PATIENT RESOURCES

None available

NGC STATUS

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